

A phase II study to evaluate subcutaneous abatacept vs. placebo in diffuse cutaneous systemic sclerosis—a double-blind, placebo-controlled, randomized controlled trial

ASSET

[IM101-344]

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PROTOCOL SYNOPSIS

Protocol Title:	A phase 2 study to evaluate subcutaneous abatacept vs. placebo in diffuse cutaneous systemic sclerosis – a double-blind, placebo-controlled, randomized controlled trial
Sponsor	This is an Investigator-Initiated study and Dinesh Khanna will be the Sponsor. Bristol Myers Squibb will be supplying the drug/placebo and study funding. The mechanistic study is supported by DAIT, NIAID, and NIH as part of the Clinical ACE grant to UM
Site Numbers:	35 sites in the US, Canada and Europe
Research Hypothesis:	SC abatacept is safe and shows evidence of efficacy (improvement in modified Rodnan score [mRSS]) in patients with diffuse cutaneous systemic sclerosis (dcScs) compared to matching placebo.
Study Schema: Drugs / Doses / Length of Treatment	125 mg SC abatacept vs SC placebo administered weekly for 12 months with a 6 month open-label extension
Study Objectives:	
<ul style="list-style-type: none"> Primary: 	<ul style="list-style-type: none"> To assess the safety of treatment with abatacept 125 mg SC versus placebo SC given every week To assess the efficacy of treatment with abatacept 125 mg SC versus placebo SC given every week on skin fibrosis using the mRSS
<ul style="list-style-type: none"> Secondary: 	<p>To assess the efficacy of treatment with abatacept 125 mg SC versus placebo SC given every week on:</p> <ul style="list-style-type: none"> Joint swelling and tenderness as measured by 28 joint count Patient's and physician's global assessment on a Likert scale Health-related quality of life (HRQOL) using PROMIS-29 2.0 Physical function as assessed by the scleroderma health assessment questionnaire-disability index (SHAQ-DI) Fatigue as assessed by PROMIS fatigue scale Sleep as assessed by PROMIS sleep disturbances and impairment scales Gastrointestinal symptoms as assessed by UCLA GIT 2.0

	<ul style="list-style-type: none"> • Combined Response Index in Systemic Sclerosis (CRISS) • Percent predicted forced vital capacity (FVC)
<ul style="list-style-type: none"> • Exploratory: 	<p>To assess the efficacy of treatment with abatacept 125 mg SC versus placebo SC given every week on a core set of items developed for a composite index in early dcSSc:</p> <ul style="list-style-type: none"> • Patient interference with the skin involvement in the past month on a Likert scale. New or worsened clinically significant heart disease, considered secondary to dcSSc, including congestive heart failure requiring hospitalization, new onset pulmonary hypertension requiring treatment, pericardial disease requiring intervention or exhibiting clinical decompensation, and arrhythmias and/or conduction defects requiring treatment • New renal crisis • Percent predicted carbon monoxide diffusing capacity (DLCO), corrected for hemoglobin • Significant ILD defined by a decline in forced vital capacity (FVC)% predicted $\geq 15\%$ (relative), high resolution computer tomography (HRCT) to confirm interstitial lung disease (ILD; if previous high resolution computer tomography of chest did not show ILD) and FVC% predicted below 80% predicted • Change from baseline in body mass index • Digital ulcer net burden as assessed by the investigator during the trial (baseline to 12 months) • Pain intensity due to dcSSc over the past week on a 0-150 mm VAS
Ancillary Objective	To validate a new PRO for Scleroderma-related Skin Symptoms (PRO-SRSS) in a subset of patients, identified based on the incorporation of this aim in the amended protocol.
Study Design:	Double-blind randomized placebo-controlled trial. Subjects will be randomized 1:1 to abatacept or placebo within stratum defined by dcSSc disease duration (≤ 18 months vs. > 18 to ≤ 36 months).

Accrual Goal: (Total number of participants)	Approximately 121 screened participants to randomize 86 patients
Accrual Rate: (Number of participants expected per month)	6-8 / month
Follow-Up:	12 month double-blind follow-up, followed by 6 month open-label follow-up, with a 30-day follow-up telephone after permanent discontinuation of study medication.
Correlative Studies: (PK/PD, etc.)	Skin and blood biomarkers
Inclusion Criteria:	<ol style="list-style-type: none"> 1. Signed written informed consent 2. Diagnosis of SSc, as defined using the 2013 American College of Rheumatology/ European Union League Against Rheumatism classification of SSc 3. dcSSc as defined by LeRoy and Medsger 4. Disease duration of ≤ 36 months (defined as time from the first non-Raynaud phenomenon manifestation) <ul style="list-style-type: none"> For disease duration of ≤ 18 months <ul style="list-style-type: none"> • ≥ 10 and ≤ 35 mRSS units at the screening visit For disease duration of >18-36 months <ul style="list-style-type: none"> • ≥ 15 and ≤ 45 mRSS units at the screening visit and one of the following: <ul style="list-style-type: none"> ○ Increase ≥ 3 in mRSS units compared with the last visit within previous 1–6 months ○ Involvement of one new body area with ≥ 2 mRSS units compared with the last visit within the previous 1–6 months ○ Involvement of two new body areas with ≥ 1 mRSS units compared with the last visit within the previous 1–6 months ○ Presence of 1 or more Tendon Friction Rub

	<ol style="list-style-type: none"> 5. Age ≥ 18 years at the screening visit 6. If female of childbearing potential, the patient must have a negative pregnancy test at screening and baseline visits 7. Oral corticosteroids (≤ 10 mg/day of prednisone or equivalent) and NSAIDs are permitted if the patient is on a stable dose regimen for ≥ 2 weeks prior to and including the baseline visit. 8. ACE inhibitors, calcium-channel blockers, proton-pump inhibitors, and/or oral vasodilators are permitted if the patient is on a stable dose for ≥ 2 weeks prior to and including the baseline visit
Exclusion Criteria:	<ol style="list-style-type: none"> 1. Rheumatic disease other than dcSSc; it is acceptable to include patients with fibromyalgia and scleroderma-associated myopathy 2. lcSSc or sine scleroderma at the screening visit 3. Major surgery (including joint surgery) within 8 weeks prior to screening visit 4. Infected ulcer prior to randomization 5. Treatment with any investigational agent within ≤ 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of the baseline visit 6. Severe (MRSS 3) skin on the inner aspects of thighs, upper arms, and abdomen 7. Previous treatment with cell-depleting therapies, including investigational agents, including but not limited to, CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and ABA 8. Anti-CD20, and cyclophosphamide within 12 months prior to baseline visit. 9. Use of Intravenous Immunoglobulin (IVIG) within 12 weeks prior to baseline visit 10. Previous treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation 11. Immunization with a live/attenuated vaccine within ≤ 4 weeks prior to the baseline visit 12. Treatment with methotrexate, hydroxychloroquine, cyclosporine A, azathioprine, mycophenolate mofetil rapamycin, colchicine, or D-penicillamine, within ≤ 4 weeks prior to the baseline visit 13. Treatment with etanercept within ≤ 2 weeks, infliximab,

	<p>certolizumab, golimumab, ABA or adalimumab within ≤ 8 weeks, anakinra within ≤ 1 week prior to the baseline visit</p> <p>14. Pulmonary disease with FVC $\leq 50\%$ of predicted, or DLCO (uncorrected for hemoglobin) $\leq 40\%$ of predicted at the screening visit</p> <p>15. Pulmonary arterial hypertension (PAH) as determined by right heart catheterization or on PAH approved medications for PAH. It is acceptable to use PDE-5 inhibitors for Raynaud's and digital ulcers.</p> <p>16. Subjects at risk for tuberculosis (TB). Specifically excluded from this study will be participants with a history of active TB within the last 3 years, even if it was treated; a history of active TB greater than 3 years ago, unless there is documentation that the prior anti-TB treatment was appropriate in duration and type; current clinical, radiographic, or laboratory evidence of active TB; and latent TB that was not successfully treated (≥ 4 weeks).</p> <p>17. Positive for hepatitis B surface antigen prior to the baseline visit</p> <p>18. Positive for hepatitis C antibody, if the presence of hepatitis C virus was also shown with polymerase chain reaction or recombinant immunoblot assay prior to baseline visit.</p> <p>19. Any of the following prior to the baseline visit: Hemoglobin < 8.5 g/dL; WBC $< 3,000/\text{mm}^3$ ($< 3 \times 10^9/\text{L}$); platelets $< 100,000/\text{mm}^3$ ($< 3 \times 10^9/\text{L}$); serum creatinine $> 2 \times \text{ULN}$; serum ALT or AST $> 2 \times \text{ULN}$</p> <p>20. Any other laboratory test results that, in the opinion of the investigator, might place a participant at unacceptable risk for participation in the study.</p> <p>21. The following medical history and concurrent diseases:</p> <ul style="list-style-type: none"> • Subjects who are impaired, incapacitated, or incapable of completing study-related assessments • Subjects with active vasculitis of a major organ system • Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease, whether or not related to SSc and which, in the opinion of
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	<p>the investigator, might place a participant at unacceptable risk for participation in the study</p> <ul style="list-style-type: none"> • Subjects with a history of cancer in the last 5 years, other than non-melanoma skin cell cancers cured by local resection or carcinoma in situ. Existing non-melanoma skin cell cancers should be removed, the lesion site healed, and residual cancer ruled out before administration of the study drug • Subjects who currently abuse drugs or alcohol • Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infections at the time of potential enrollment, including participants with evidence of human immunodeficiency virus (HIV) detected during screening • Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months prior to screening • Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (e.g., chronic pyelonephritis, osteomyelitis, or bronchiectasis) <p>22. Patients with a history of anaphylaxis to abatacept</p>
Criteria for Evaluation: (Efficacy, safety, stopping rules, etc.)	Evaluation every 3 months
Statistics:	<p>Sample Size. This phase 2 study is primarily sized based on practical considerations, rather than a desired power for a pre-specified difference. We anticipate a 15% drop-out rate and thus plan to randomize 86 participants to achieve 74 analyzable participants. With the proposed sample size, there is at least 80% power to detect a 24% treatment difference in proportions of participants with adverse events with a two-sided Type I error of 5% and a placebo rate of 70%. For continuous outcomes, the proposed sample size provides at least 80% power to detect an effect size of at least 0.66 with a two-sided Type I</p>

	<p>error of 5%. This effect size (treatment difference / pooled SD) translates into a treatment difference in change from baseline to month 12 in mRSS of 5.3 with a SD of 8.0 points.</p> <p>Safety Analysis. All safety analyses will be performed on the Safety Population, defined as all participants who were randomized and received at least one dose of the study drug. Subjects will be analyzed by the treatment received. Safety measures including AEs, clinical laboratory tests, vital signs, physical exams, and concomitant medication usage will be summarized descriptively. For quantitative variables, descriptive statistics including number of observations, mean, median, standard deviation and range will be given for the values themselves as well as for change from baseline by treatment group at each study visit. Qualitative variables will be summarized using counts and percentages by treatment group at each study visit.</p> <p>Efficacy Analysis. The main population for efficacy will be the modified intention-to-treat population (MITT), defined as all participants randomized and receive at least one dose of study drug. Subjects will be analyzed by assigned treatment. No adjustment for multiplicity will be made. The change from baseline in mRSS will be summarized for each treatment group by study visit. Differences from baseline will be calculated and summarized as above, with a 95% confidence interval for the mean. The difference between treatment groups in change from baseline to Month 12 in mRSS scores will be evaluated using an ANCOVA model with terms for treatment group, duration of dcSSc disease (stratification factor) and baseline mRSS score.</p> <p>Secondary and exploratory efficacy variables that are continuous measures will be analyzed similarly to the primary efficacy analyses. Exploratory efficacy measures that are categorical will be analyzed using the chi-square test. They will be summarized by frequencies and percents, overall, and by treatment group. P-values from the secondary and exploratory efficacy analyses will be considered nominal. The sensitivity of the results for mRSS to missing data assumptions will be explored as outlined in the Statistical Analysis Plan (SAP) for the study. Examination of treatment effects over time may be examined</p>
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	using methods appropriate for repeated observations depending on sample sizes. Additional exploratory analyses may be performed and will be defined and outlined in the SAP for the study.
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1 INTRODUCTION

Systemic sclerosis (Scleroderma, SSc) is one of the most fatal rheumatic diseases, and is associated with substantial morbidity¹ and many detrimental effects on health-related quality of life. Recent years have seen a revolution in the development and validation of outcome measures²⁻⁴ and refinement of trial methodology in SSc⁵. This is paralleled by an increased understanding of the pathogenesis of SSc^{6,7} and development of targeted therapies^{8,9}. Modified Rodnan Skin Score (mRSS) a measure of skin thickness^{10,11}, has been used as the primary outcome measure in clinical trials of diffuse cutaneous SSc (called diffuse SSc or dcSSc from here on). Food and Drug Administration considers improvement in mRSS as an approvable end point.

Several observations support the role of activated T cells in the pathogenesis of SSc. Skin biopsies obtained from SSc patients early in their disease demonstrate a perivascular, mononuclear cell infiltrate comprised of T cells and macrophage. T cell activation is a prominent feature in SSc, as demonstrated by the presence of increased numbers of T cells bearing activation markers, such as IL-2 receptor, as well as elevated levels of cytokines such as IL-2, IL-4, IL-6, and IL-17 in the peripheral blood of patients with SSc. In addition, oligoclonal T cells have been demonstrated in the skin and bronchoalveolar lavage fluid from patients with SSc, implicating specific antigen-driven T cell proliferation in the disease process. T and B lymphocyte interactions are important in the pathogenesis of SSc, and T cells have been shown to be essential for the production of autoantibodies in this disease. Recent data also indicates an imbalance between Th17 and T regulatory cells in patients with SSc. Th17 cell concentrations are elevated in the peripheral blood of patients with SSc, while T regulatory cells are reduced in skin lesions from SSc patients. Finally, treatments directed against activated T cells, such as cyclosporine A, or depletion of T cells have resulted in skin softening in patients with SSc.

A recent pilot study evaluated the effect of blockade of T cell co-stimulation with intravenous abatacept in patients with dSSc showed efficacy and not serious or unanticipated adverse events. Therefore, we aim to perform a phase II, multi-center double-blind randomized controlled trial of subcutaneous abatacept vs. placebo in patients with early dcSSc.

1.1 Summary of Results of Investigational Program

1.1.1 Pharmacology of Abatacept

Abatacept is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 and a fragment (hinge- CH2-CH3 domains) of the Fc domain of human IgG1 that has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity.

Abatacept is the first drug in a new class of agents termed “selective costimulation modulators.” Abatacept binds specifically to the CD80 and CD86 molecules, proteins prominently displayed on the surface of antigen-presenting cells (APCs). Activation of naive T cells during an immune response requires two stimuli from APCs. The first signal is antigen-specific; antigens are presented by APCs, with the signal transmitted to the T cell through the T cell’s antigen receptor. The second, or costimulatory, signal is not antigen-specific and is delivered following the engagement of a costimulatory ligand on the APC with a cognate receptor on the T cell.

A key costimulatory receptor on T cells is CD28. CD28 is constitutively expressed on resting T cells and binds to both CD80 (B7-1) and CD86 (B7-2) on the APC¹²⁻¹⁵. A costimulatory signal is required not only for the full activation of naive T cells, but also may be required for the survival of memory and autoimmune effector cells^{16, 17}. At 24 to 48 hours following T cell activation, the T cell expresses CTLA4 on its surface, which engages the CD80 and CD86 molecules on the APC surface interfering with CD28’s ability to bind to its ligands on the APC; CD80 and CD86 preferentially bind to CTLA4 with a much higher avidity than with CD28. Although the precise mechanisms are as yet unclear, CTLA4 expression is associated with a decrease in T cell activation.

After the T cell activity has been dampened, the CTLA4 recycles into the T cell’s cytoplasm. The CTLA4 section of abatacept binds specifically to CD80 and CD86 (B7-1 and B7-2, respectively) and down-modulates the CD28-mediated costimulation of T cells. Thus, abatacept uses a segment of a molecule that is part of the normal immune homeostatic mechanism to suppress T cell activity involved in the immunopathogenesis of autoimmune diseases. The FC region of abatacept was engineered with several point mutations designed to inactivate it. Because of these changes, abatacept does not mediate pathways such as antibody-dependent cell cytotoxicity or complement-dependent cytotoxicity¹⁸.

1.1.2 Human Pharmacokinetics of Abatacept

Single subcutaneous (SC) doses of abatacept (50 to 150 mg) demonstrated approximately dose proportional PK in healthy adult participants¹⁹. Following administration of single doses of 50 to 150 mg of abatacept, the mean C_{max} increased from 3.5 to 10.7 µg/mL and the geometric mean AUC (INF) increased from 1490 to 4270 µg·hour/mL. The median time to occurrence of C_{max} (T_{max}) following SC administration ranged between 48 and 168 hours. Mean T_{1/2} values in healthy participants ranged

from 11.2 to 14.7 days. $T_{1/2}$ values from this study were comparable with the $T_{1/2}$ values obtained with abatacept administered IV to participants with RA (13 to 14 days)²⁰. The fact that $T_{1/2}$ values following SC dosing were comparable to $T_{1/2}$ values obtained after IV dosing suggests that the elimination characteristics of abatacept were not altered following SC administration.

A double-blind, randomized, placebo-controlled, parallel-group, multiple-dose study (IM101063) assessed the steady-state trough serum concentrations of abatacept following SC administration in participants with RA²¹. Subjects were randomized to receive either abatacept or placebo in 1 of 5 parallel groups based on body weight obtained at the screening visit (Table 1.3.2A). The SC dose regimens were selected to target trough levels between 10-30 ug/mL, which was associated with efficacy with the IV formulation.

Table 1.3.2A. IM101063 Treatment Groups Based on Body Weight

Treatment Group	Subject weight (kg)	IV dose on Day 1 (mg)	SC dose weekly for 12 weeks (mg)	SC injection volume (mL)
1	< 60	500	75	0.6
2	< 60	500	125	1
3	60 - 100	750	125	1
4	> 100	1000	125	1
5	> 100	1000	200	0.6 + 1.0

Source: Clinical Study report for IM101063: A Study To Assess The Steady-State Trough Serum Concentrations, Safety, And Immunogenicity Of Abatacept (BMS-188667) Administered Subcutaneously In Subjects With Active Rheumatoid Arthritis Who Are Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs). Bristol-Myers Squibb; 2008. Document Control No. 930025069.

On Day 1, participants received a single IV infusion (loading dose) of abatacept or placebo, based on their weight range. Approximately 1 hour after the completion of the IV infusion, participants received their assigned SC dose of abatacept or placebo. Abatacept or placebo was administered weekly by the SC route, at the same dose as the SC dose on Day 1, for a total of 12 SC injections. Blood samples for PK analysis were collected on Day 1 prior to and at the end of the IV infusion. In addition, blood samples were collected prior to each weekly SC dose of abatacept.

Steady-state trough serum concentrations were achieved after ~ 4 to 5 weeks following the combined regimen of a single IV loading dose and weekly SC injections. With the exception of treatment group 4 (abatacept 125 mg SC weekly dose for participants weighing > 100 kg), the mean steady-state trough concentrations across all other treatment groups appeared to be comparable.

However, to truly represent the steady-state serum levels from SC administration without the contribution of the IV loading dose, Cmin values on Days 71-85 were selected, since contribution from IV was expected to be negligible. Comparison of mean steady-state trough concentrations on Day 71, 78 and 85 indicated that abatacept did not appear to accumulate following weekly dosing (Table 1.3.2B).

Table 1.3.2B. Summary Statistics for Abatacept Steady-State Cmin Values on Days 71, 78, and 85 - IM101063

Treatment Group	Study Day	n	Cmin (µg/mL) Geometric Mean (CV%)	Cmin (µg/mL) Median (Min, Max)
1 (500 mg IV / 75 mg SC)	71	7	22.64 (20.13)	20.92 (17.06, 29.84)
	78	7	21.66 (19.99)	22.40 (16.01, 28.93)
	85	7	23.62 (31.63)	21.91 (18.24, 39.60)
2 (500 mg IV / 125 mg SC)	71	4	28.03 (42.13)	32.57 (13.73, 43.30)
	78	3	34.17 (29.49)	33.10 (25.97, 46.40)
	85	3	36.73 (31.64)	37.50 (26.26, 50.30)
3 (750 mg IV / 125 mg SC)	71	26	24.05 (40.65)	26.53 (7.97, 54.11)
	78	23	24.41 (52.35)	27.54 (5.40, 68.90)
	85	25	24.93 (38.42)	26.01 (9.57, 53.80)
4 (1000 mg IV / 125 mg SC)	71	3	16.22 (24.39)	15.15 (13.37, 21.07)
	78	5	11.57 (32.25)	13.20 (6.89, 16.33)
	85	5	13.01 (41.35)	13.30 (6.66, 22.73)
5 (1000 mg IV / 200 mg SC)	71	5	26.52 (56.53)	26.20 (8.68, 55.20)
	78	5	29.21 (52.96)	40.40 (8.04, 57.10)
	85	5	27.53 (58.87)	29.01 (8.74, 62.00)

Source: Clinical Study report for IM101063: A Study To Assess The Steady-State Trough Serum Concentrations, Safety, And Immunogenicity Of Abatacept (BMS-188667) Administered Subcutaneously In Subjects With Active Rheumatoid Arthritis Who Are Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs). Bristol-Myers Squibb; 2008. Document Control No. 930025069. Supplemental Table S.8.2.2.

n=number of observations

Steady-state pharmacokinetic parameters of abatacept after weekly SC administration were determined between the SC dosing interval from Day 71 to 78. Cmax and AUC (TAU) appear to be comparable in Treatment Groups 1, 3 and 5 (Table 1.3.2C).

Table 1.3.2C. Summary Statistics for Abatacept Steady-State Pharmacokinetic Parameters - IM101063

Treatment Group	Pharmacokinetic Parameter	
	C _{max} (µg/mL) Geometric Mean (CV%)	AUC(TAU) (µg*h/mL) Geometric Mean (CV%)
1 (500mg IV / 75mg SC)	n = 7 26.3 (29.5)	n = 7 4066 (22.2)
2 (500mg IV / 125mg SC)	n = 4 34.9 (46.6)	n = 3 6699 (20.7)
3 (750mg IV / 125mg SC)	n = 26 31.9 (42.8)	n = 24 4607 (38.6)
4 (1000mg IV / 125mg SC)	n = 5 14.7 (44.3)	n = 4 2555 (30.1)
5 (1000mg IV / 200mg SC)	n = 5 41.7 (41.2)	n = 5 5849 (40.5)

Source: Clinical Study report for IM101063: A Study To Assess The Steady-State Trough Serum Concentrations, Safety, And Immunogenicity Of Abatacept (BMS-188667) Administered Subcutaneously In Subjects With Active Rheumatoid Arthritis Who Are Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs). Bristol-Myers Squibb; 2008. Document Control No. 930025069. Supplemental Table S.8.2.3.

n = number of participants, TAU = 7 days

C_{max} and AUC(TAU) were calculated between a SC dosing intervals from Day 71 to Day 78 profile.

1.1.3 Clinical Safety with Abatacept SC Formulation

The safety experience with SC abatacept was characterized in 2 ways: events during cumulative SC period and events during the comparative SC/IV period. The key safety findings based on these analyses are listed below²².

The **cumulative SC** period, during which 1879 participants received SC abatacept for a total exposure of 1945.60 person-years (p-y), was based on cumulative (short term/ long term) pooled data of the Phase 2 and 3b studies from:

- All participants in the SC abatacept treatment group in the ST period of IM101174
- All participants in the IV abatacept treatment group in the ST period of IM101174 (including the anti-TNF failure substudy) who were treated with SC abatacept in the LT period, from the start of SC abatacept in the LT period
- All participants in ST abatacept treatment groups from IM101063
- All participants in the ST placebo group from IM101063 who were treated with SC abatacept in the LT period, from the start of SC abatacept in the LT period
- All treated participants in IM101167, IM101173, and IM101185

No new safety signal was identified for SC abatacept across the parameters of death, SAEs, AEs/SAEs leading to discontinuation, treatment-related AE/SAEs, and overall AEs.

Table 1.1.3A: Overall Safety for the Cumulative SC Abatacept Period

	Number (%) of Subjects N = 1879	Incidence Rate (per 100 p-y)	Poisson 95% Confidence Interval
Deaths	9 (0.5%)	0.46	(0.24, 0.89)
SAEs	161 (8.6%)	8.63	(7.39, 10.07)
AEs	1267 (67.4%)	144.36	(136.63, 152.53)
AEs leading to discontinuation	46 (2.4%)	2.37	(1.78, 3.16)

Source: Subcutaneous abatacept summary of clinical safety. Bristol-Myers Squibb, 2010. Document Control No. 930043734.

The subgroup analyses by body weight did not identify a differential safety profile for any of the weight groups, including the 24% of participants weighing less than 60 kg. No new safety signal was identified for AEs of special interest:

- Infection and infestation AEs were reported in 756 (40.2%) participants with an incidence rate (per 100 p-y of exposure) of 54.94. The majority of infections were of mild to moderate intensity. The cumulative SC period incidence rate of infections and infestation AEs was consistent with previous IV abatacept experience.
- Malignancies were reported in 20 (1.1%) participants with an incidence rate (per 100 p-y of exposure) of 1.04. Malignancies excluding non-melanoma skin cancer (NMSC) were reported in 9 (0.5%) participants with an incidence rate (per 100 p-y of exposure) of 0.46. The cumulative SC period incidence rate of malignancies was consistent with previous IV abatacept experience.
- Pre-specified autoimmune events were reported in 17 (0.9%) participants with an incidence rate (per 100 p-y of exposure) of 0.88; most were of mild to moderate intensity with the exception of 1 severe event (vasculitis). One pre-specified autoimmune event was reported as serious (sarcoidosis of moderate intensity), which led to premature discontinuation. The cumulative SC period incidence rate of autoimmune events was consistent with underlying disease and previous IV abatacept experience.
- Pre-specified local injection site reactions were reported in 58 (3.1%) participants with an incidence rate (per 100 p-y of exposure) of 3.09. Most local injection site reactions were of mild to moderate intensity; 1 event (severe injection site reaction) was serious and led to premature discontinuation.
- Systemic injection reaction AEs were reported in 131 (7.0%) participants with an incidence rate (per 100 p-y of exposure) of 7.21. Most events were of mild to moderate intensity; none were serious; 1 event (moderate angioedema) led to premature discontinuation.

- Pre-specified acute- and peri-infusional AEs were reported in 15 (1.6%) and 35 (3.6%) participants, respectively; all events were of mild to moderate intensity with the exception of 1 severe event (headache).
- The safety profile of SC abatacept was also assessed under clinical scenarios that might increase the development of immunogenicity and determined the consequences of treating with SC abatacept (e.g., no IV load, monotherapy without MTX, prolonged withdrawal of therapy, switch from IV to SC abatacept).

The **comparative SC/IV period** (ST period of IM101174), which provided a direct comparison of the safety data between the SC and IV abatacept formulations. The cumulative SC period did not have a comparator group to provide context for safety assessment; an evaluation was made of the cumulative SC period to the safety events reported in the Summary of Clinical Safety submitted to the FDA (June 2010)²³. Overall, consistent safety profiles were observed for the SC abatacept and IV abatacept groups across the parameters of death, SAEs, AEs/SAEs leading to discontinuation, treatment-related AE/SAEs, and overall AEs (Table 1.1.3B).

Table 1.1.3B. Overall Safety for the Comparative SC/IV Abatacept Population - IM101174 (short-term Period)

	Number (%) of Subjects	
	SC Abatacept N = 736	IV Abatacept N = 721
Deaths	2 (0.3%)	5 (0.7%)
SAEs	31 (4.2%)	35 (4.9%)
AEs	493 (67.0%)	470 (65.2%)
AEs leading to discontinuation	15 (2.0%)	25 (3.5%)

Source: Subcutaneous Abatacept Summary of Clinical Safety. Bristol-Myers Squibb, 2010. Document Control No. 930043734.

The subgroup analyses by body weight did not identify a differential safety profile for any of the weight groups, including the 24% of participants weighing less than 60 kg indicating that the higher exposures (Cmin) due to the fixed dosing regimen did not result in any additional safety risks.

The safety profiles observed for SC abatacept and IV abatacept were consistent for AEs of special interest:

- Infection and infestation AEs were reported in 234 (31.8%) and 221 (30.7%) participants in the SC abatacept and IV abatacept groups, respectively. The majority of infections were of mild to moderate intensity.

- Malignancies were reported in 3 (0.4%) and 5 (0.7%) participants in the SC abatacept and IV abatacept groups, respectively. Of these, 2 malignancies from each group were non-melanoma skin cancers (NMSC).
- Pre-specified autoimmune events were reported in 7 (1.0%) and 6 (0.8%) participants in the SC abatacept and IV abatacept groups, respectively; all events were of mild to moderate intensity.
- Pre-specified local injection site reactions were reported in 19 (2.6%) and 18 (2.5%) participants in the SC abatacept and IV abatacept (i.e., SC placebo) groups, respectively. All pre-specified local injection site reactions were of mild to moderate intensity; none led to premature discontinuation.
- Systemic injection reaction AEs were reported in 56 (7.6%) and 56 (7.8%) participants in the SC abatacept and IV abatacept groups; respectively. No serious systemic injection reactions were reported in the SC abatacept group; 1 participant in the IV abatacept group had serious systemic injection reactions (nausea and headache). In both treatment groups, most pre-specified systemic injection reaction AEs were of mild or moderate intensity; none led to premature discontinuation.
- Pre-specified acute infusional AEs were reported in 20 (2.7%) and 16 (2.2%) participants in the SC abatacept and IV abatacept groups, respectively. In both treatment groups, most of the pre-specified acute infusional events were of mild to moderate intensity; only 1 event in each treatment group, both reported on Day 1, led to premature discontinuation.

Data from the SC abatacept clinical development program indicates that the SC abatacept formulation did not lead to increased immunogenicity and when present did not affect safety.

1.1.4 Drug-Related Adverse Events

Injection Site Reactions in Adult RA Patients Treated with Subcutaneous Abatacept

IM101-174 compared the safety of abatacept including injection site reactions following subcutaneous or intravenous administration. The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous abatacept group and the intravenous abatacept group (subcutaneous placebo), respectively. All these injection site reactions (including hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

Immunogenicity in Adult RA Patients Treated with Subcutaneous Abatacept

IM101-174 compared the immunogenicity to abatacept following subcutaneous or intravenous administration. The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with previous experience, and there was no correlation of immunogenicity with effects on pharmacokinetics, safety, or efficacy.

Immunogenicity and Safety of Subcutaneous Abatacept Administration as Monotherapy without an Intravenous Loading Dose

IM101-173 was conducted to determine the effect of monotherapy use of abatacept on immunogenicity following subcutaneous administration without an intravenous load in 100 RA patients, who had not previously received abatacept or other CTLA4 Ig, who received either subcutaneous abatacept plus methotrexate (n=51) or subcutaneous abatacept monotherapy (n=49). No patients in either group developed anti-product antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

Immunogenicity and Safety of Subcutaneous Abatacept upon Withdrawal (Three Months) and Restart of Treatment

IM101-167 in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of abatacept subcutaneous treatment on immunogenicity in RA patients treated concomitantly with methotrexate. One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous abatacept or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label abatacept treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 patients who continued to receive subcutaneous abatacept developed anti-product antibodies compared to 7/73 (9.6%) of patients who had subcutaneous abatacept withdrawn during this period. Half of the patients receiving subcutaneous placebo during the withdrawal period received a single intravenous infusion of abatacept at the start of period 3 and half received intravenous placebo. At the end of period 3, when all patients again received subcutaneous abatacept, the immunogenicity rates were 1/38 (2.6%) in the group receiving subcutaneous abatacept throughout, and 2/73 (2.7%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions, and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. The safety observed in this study was consistent with that observed in the other studies.

1.1.5 Clinical Efficacy of Abatacept Subcutaneous Formulation

The clinical development program for SC abatacept for rheumatoid arthritis included 4 Phase 3b efficacy, safety, and immunogenicity studies (IM101167, IM101173, IM101174 and IM101185) plus 2 clinical pharmacology studies (IM101013 and IM101063). Overall, the efficacy data from the SC abatacept development program demonstrated that the efficacy profile of SC abatacept is comparable to IV abatacept²⁴.

The key efficacy results were:

- The clinical efficacy of a fixed-dose of SC abatacept 125 mg weekly (following a single weight-tiered IV loading dose on Day 1) was non-inferior to weight-tiered IV abatacept, as assessed by the primary endpoint of ACR 20 at Day 169 (point estimates of 76.1% vs 75.7%, respectively). The non-inferiority margin ensured that SC abatacept maintained at least 70% of effectiveness of IV abatacept. The results from this study established that SC abatacept preserves at least 83% of the effect of IV abatacept (Study IM101174).
- The magnitude of clinical response starting at Day 15 and up to 6-months, across all pre-specified efficacy endpoints (ACR 20, ACR 50, ACR 70, DAS28 remission, LDAS) and physical function endpoint (HAQ) was comparable between SC abatacept and IV abatacept (Study IM101174).
- Clinical efficacy as measured by ACR 20 and HAQ response was similar between SC abatacept and IV abatacept within all weight subgroups, as well as all other subgroups assessed (Study IM101174).
- Clinical efficacy was maintained with LT administration of SC abatacept for up to 18 months (Studies IM101174, IM101173, IM101167, and IM101185).
- Clinical efficacy achieved after either ST or LT IV abatacept therapy was maintained upon switch to SC abatacept (Studies IM101174 LT and IM101185, respectively).
- Based on reduction in DAS28-CRP score over time and at Day 85 (relative to baseline) in 2 studies conducted in an open-label setting, the clinical efficacy of SC abatacept with or without IV loading dose appeared to be similar; indicating that the IV loading dose at Day 1 may not be essential for obtaining early onset of action (Studies IM101167 and IM101173, respectively).
- The clinical efficacy of SC abatacept also appears to be similar upon re-initiation of SC abatacept with or without IV loading dose, based on reduction in DAS28-CRP score over time (Study IM101167).

1.2 Overall Risk/Benefit Assessment

This is a proof-of-concept phase 2 study to assess safety and efficacy of abatacept in patients with dSSc. Systemic sclerosis (Scleroderma, SSc) is one of the most fatal rheumatic diseases, and is associated with substantial morbidity and many detrimental effects on health-related quality of life. There are no Food and Drug Administration (FDA) approved drugs for SSc. Please see Section 1.6 for more details.

1.3 Research Hypothesis

SC abatacept is safe and shows evidence of efficacy in patients with dSSc compared to matching placebo.

1.4 Study Rationale

1.4.1 Role of T cells in the pathogenesis of SSc

CD4+ T cells are central to the pathogenesis of a range of autoimmune diseases, both through their role in activating B cell differentiation and autoantibody production, and through secretion of cytokines. T cell subsets can also protect against or attenuate autoimmunity through a variety of regulatory mechanisms. The CD4+ T cell population contains distinct subsets classified according to their program of cytokine secretion, such as the Th1, Th2 and Th17 cells, regulatory T cells (Tregs), follicular-helper T cells, and additional subsets including bi-functional subsets that overlap between more than one Th population. Activation of all subsets of CD4+ T cells requires delivery of at least 2 signals to the T cell, one through recognition of antigen-MHC and the second through co-stimulation, primarily by binding of the CD28 ligands B7.1 and B7.2 (CD80 and CD86) to CD28 on the T cell membrane.

Substantial evidence supports the concept that T cells play a key role in the pathogenesis of SSc, including cutaneous disease and at least some of the visceral complications. Skin biopsies obtained from SSc patients early in their disease demonstrate a perivascular, mononuclear cell infiltrate comprised of T cells and macrophages²⁵⁻²⁷. T cells are the dominant population of lymphocytes in the skin, and are activated²⁶. T cell infiltration correlate with the skin thickening, suggesting a relation between inflammation and fibrosis²⁸. The expression of inducible costimulator (ICOS), expressed on activated T cells, is elevated in patients with early dcSSc²⁹. T cells transferred from bleomycin-treated mice (a mouse model of SSc) to healthy animals induces skin thickening³⁰. Also, the T lymphocytes in SSc tissue overexpress TNF receptor II and that these cells, when costimulated with TNF- α , trigger collagen production by releasing profibrotic cytokines³¹.

Controversy and ambiguity exists, however, regarding which Th subset may be pathogenic in SSc, with the focus largely on the Th2 and Th17 cells^{32, 33}. Th2 cells, defined by their production of IL-4, have been implicated in SSc because some of their cytokine products, such as IL-13, are pro-fibrotic³⁴⁻³⁶. Moreover, Th2 cells are found in excess in the blood of patients with SSc, and in both cutaneous and pulmonary disease. We showed that Th2 cells in bronchoalveolar lavage fluid in SSc associated interstitial lung disease declined during treatment with imatinib^{37, 38}. Th1 mechanisms appear to be anti-fibrotic^{32, 39}.

The more recently described Th17 subset is also expanded in SSc blood and skin, and has been suspected to be pathogenic⁴⁰⁻⁴⁴, although Th17 cytokines are not viewed as pro-fibrotic. One report suggests that Th22 cells, as well as Th2 and Th17, are expanded in patients with interstitial lung disease and SSc⁴⁵. Important new evidence suggests that although prevalent in SSc skin, the Th17 cells might actually be protective against skin fibrosis⁴⁶. Unlike IL-4+ cells, the IL-17A+ cells are in proximity to myofibroblasts in SSc skin, but in vitro IL-17A does not induce but rather inhibits myofibroblast

differentiation, and instead increases collagenase expression. An inverse correlation was found between the density of IL-17A+ cells and the extent of skin thickness.

The genome-wide association studies in SSc⁴⁷ have led to the discovery of over 30 genes and gene regions, including both human leukocyte antigen (HLA) and non-HLA genes, identifying as SSc susceptibility loci. Most of these genes are associated with lymphocyte activation and signaling (e.g. TNIP1⁴⁸), innate immunity (e.g. IRF8⁴⁹), transcription factors (e.g. STAT4⁵⁰) and cytokine receptors (e.g. IL2RA⁴⁷). T cells from peripheral blood of women with SSc are activated, as judged by overexpression of CD40-ligand due to DNA demethylation⁵¹ and that the level of DNA methyltransferase 1 is significantly decreased in patients with SSc⁵². Recently cytosine-phosphate-guanosine demethylation within the CD40L gene on the inactive X chromosome has been documented to contribute to CD40L overexpression in CD4+ T lymphocytes from female SSc patients⁵¹ and could explain the female dominance in this condition.

In summary, available data suggests that Th2 cells are pathogenic and Th17 cells protective in SSc^{32, 39}. However, there are large knowledge gaps related in part to small sample sizes of most prior studies, lack of longitudinal data (other than serial measurements of bronchoalveolar lavage T cells and IL-4-producing cells in a small cohort of patients who received imatinib in an open label fashion for scleroderma lung disease³⁸), limited data concurrently obtained from skin and blood, and lack of data prospectively acquired during a clinical trial of an agent that is expected to affect T cells. The study proposed is designed to address these gaps, and to shed light on the immunopathogenesis of SSc as well as on predictors of response to an immunomodulatory treatment.

1.4.2 ABA in SSc

The co-stimulatory molecules expressed by activated T cells represent a unique target for biologic activity in SSc. ABA is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 and a fragment (hinge- CH2-CH3 domains) of the Fc domain of human IgG1 that has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity. ABA is the first drug in a new class of agents termed “selective costimulation modulators.” ABA is approved by the Food and Drug Administration for the treatment of rheumatoid arthritis (RA) and juvenile idiopathic arthritis. ABA binds specifically to the CD80 and CD86 molecules, proteins prominently displayed on the surface of antigen-presenting cells (APCs). Activation of naive T cells during an immune response requires two stimuli from APCs. The first signal is antigen-specific; antigens are presented by APCs, with the signal transmitted to the T cell through the T cell’s antigen receptor. The second, or costimulatory, signal is not antigen-specific and is delivered following the engagement of a costimulatory ligand on the APC with a cognate receptor on the T cell.

A pilot study of ABA in SSc supports undertaking a larger placebo-controlled trial with an emphasis on skin and blood biomarker⁵³ (detailed in next section). Although ABA is well established in the treatment

of RA, there is a striking dearth of data from human clinical trials regarding its mechanisms of action. There is evidence that pro-inflammatory cytokines are reduced by ABA treatment of RA⁵⁴. One study examined synovial tissue from 10 patients with RA who had responded to ABA + methotrexate, compared to 5 patients treated with only methotrexate⁵⁵. The ABA-treated patients had fewer T cells in synovial tissue, and also fewer B cells and monocytes. Pre-ABA biopsies were not examined. The idea that ABA might affect not only T cell function, but also various functions of B7.1/2(CD80/86)+ cells is supported by a study of monocytes from RA blood before and after treatment with ABA: after treatment monocytes accumulated in the blood and had reduced adhesive and migratory capacity⁵⁶. Similar effects were seen with in vitro exposure of normal human monocytes to CTLA4-Ig. Although synovial tissue was not evaluated in this study the findings imply that decreased ingress of monocytes into inflamed synovium is one of the therapeutic mechanisms of ABA, and raise the possibility that in SSc ABA could reduce monocyte ingress into lesional skin. In addition, ABA reduces the antigen-induced expression of ICOS in a murine model of arthritis⁵⁷, *ENREF_9* and inhibits antigen specific T cell proliferation and activation. ABA also strikingly inhibits antigen stimulated T cell secretion of IFN γ , IL-17 and IL-13, the latter known to be upregulated in the circulation of SSc patients, and possibly contributing to fibrosis. Some studies have suggested that ABA can also affect APCs through its binding to CD80/86, upregulating indoleamine 2,3-dioxygenase (IDO). Although a role for ABA in dendritic cells (DC)/macrophage phenotype was not supported by in vitro microarray studies comparing gene expression in ABA-stimulated APC subsets²⁷, only purified APCs were tested in these studies. More recent studies have suggested that the effect of ABA on DCs might be indirect, mediated by CTLA-4 on regulatory T cells, with CTLA4Ig stimulating FoxP3 expression in murine allografts associated with upregulated IDO in DCs²⁵. Thus, ABA can affect multiple T cell types, stimulating Treg cells while inhibiting other effector cell types and associated cytokine levels. Based on the immune abnormalities observed in SSc, others have suggested that ABA could be an effective agent in SSc^{58, 59}.

1.4.3 Pilot study

A recent single center pilot study evaluated the effect of blockade of T cell co-stimulation with intravenous abatacept in patients with dSSc. Ten patients were randomized in a 2:1 double-blinded fashion to receive IV abatacept or placebo at weeks 0, 2, 4, and every 4 weeks for a total of 24 weeks. 8 women and 2 men, mean age 42.2 years, enrolled in the study. The mean disease duration from the time of the first non-Raynaud's manifestation was 4.4 (SD 3.8) years. 7 patients were randomized to receive abatacept and 3 received placebo. At baseline, there were no significant differences in mRSS, Health Assessment Questionnaire-Disability Index (HAQ-DI), patient and physician global assessments by visual analogue scale (VAS) and pulmonary function tests (PFTs) between the two groups, although participants randomized to abatacept had shorter disease duration (2.4 vs. 8.8 years, $p=0.004$). Compared with those receiving placebo, participants treated with abatacept reported greater improvement in patient global assessment by VAS (-8 vs. -2.7, $p=0.023$). Subjects receiving abatacept

had a mean improvement of 8.6 (SD 7.5) in mRSS at week 24, which exceeds the minimal clinical important difference of 5.3⁶⁰. Patients receiving abatacept had a greater improvement in absolute mRSS compared with those receiving placebo, but this did not reach statistical significance given the small sample size (-8.6 vs -2.3, $p=0.059$). No deaths or serious adverse events related to abatacept occurred and overall the study drug was well-tolerated. This study was limited by small sample size and skewing of disease duration between those randomized to placebo vs abatacept, the latter fact implying that any differences between the two groups might be explained by natural history of improvement of cutaneous sclerosis early in disease.

Despite these limitations, our preliminary data support a potential role for abatacept in the treatment of cutaneous sclerosis in SSc. Therefore, we aim to perform a phase 2, multi-center double-blind randomized controlled trial of subcutaneous abatacept vs. placebo in patients with early diffuse cutaneous SSc.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To assess the safety of treatment with abatacept 125 mg SC versus placebo SC given every week
- To assess the efficacy of treatment with abatacept 125 mg SC versus placebo SC given every week on skin fibrosis using the modified Rodnan Skin Score (mRSS)

2.2 Secondary Objectives

To assess the efficacy of treatment with abatacept 125 mg SC versus placebo SC given every week on:

- Joint tenderness as measured by 28-tender joint count
- Joint swelling as measured by 28-swollen joint count
- Patient's and physician's global assessment on a Likert scale
- Health-related quality of life (HRQOL) using PROMIS-29 2.0
- Physical function as assessed by the scleroderma health assessment questionnaire-disability index (SHAQ-DI)
- Fatigue as assessed by the PROMIS Fatigue scale
- Sleep as assessed by the PROMIS sleep disturbance and impairment scale
- Gastrointestinal symptoms as assessed by UCLA SCTC GIT 2.0
- Combined Response Index in Systemic Sclerosis (CRISS)
- Percent Predicted forced vital capacity (FVC)

2.3 Exploratory Objectives

To assess the efficacy of treatment with abatacept 125 mg SC versus placebo SC given every week on a core set of items developed for a composite index in early dcSSc:

- Patient interference with the skin involvement in the past month on a Likert scale
- New or worsened clinically significant heart disease, considered secondary to dcSSc, including congestive heart failure requiring hospitalization, new onset pulmonary hypertension requiring treatment, pericardial disease requiring intervention or exhibiting clinical decompensation, and arrhythmias and/or conduction defects requiring treatment
- New renal crisis
- Percent predicted carbon monoxide diffusing capacity (DLCO), corrected for hemoglobin
- Change from baseline in body mass index
- Digital ulcer net burden as assessed by the investigator during the trial (baseline to 12 months)
- Pain intensity due to dcSSc over the past week on a 0-150 mm VAS

2.4 Ancillary Objective

To validate a new PRO for Scleroderma-related Skin Symptoms (PRO-SRSS) in a subset of patients, identified based on the incorporation of this aim in the amended protocol.

3 ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the participant informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment).

3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials/process (e.g., advertisements), and any other written information to be provided to participants. The investigator or sponsor should also provide the IRB/IEC with a copy of the Package Insert or product labeling information to be provided to participants, and any updates.

The investigator should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 Informed Consent

Details regarding the informed consent process are provided in the Manual of Operations. The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

3.4 Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to the Sponsor or designee, subjects should be identified by unique initials and a subject study number only. Documents that are not for submission to the Sponsor or designee (e.g., signed informed consent/assent forms) should be kept in strict confidence by the Investigator.

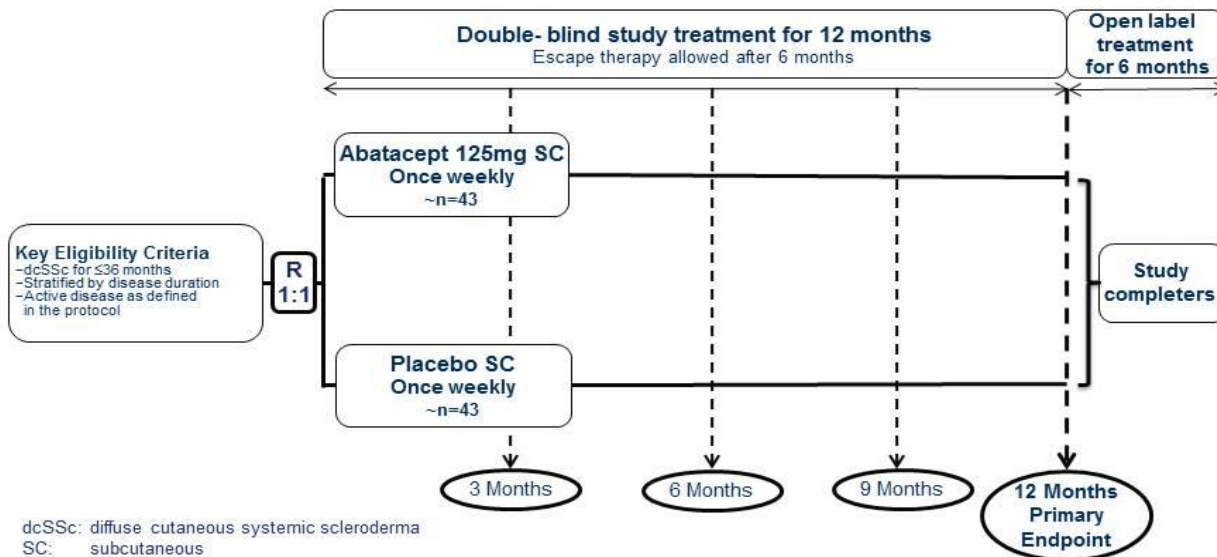
4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

This study is a randomized placebo-controlled double-blind phase 2 trial of patients with dcSSc. Eligible participants will be randomized in a 1:1 ratio to either 125 mg SC abatacept or matching placebo, stratified by duration of dcSSc disease duration (≤ 18 months vs > 18 to ≤ 36 months). Study participants will be treated for 12 months on double-blind study medication, followed by an additional 6 months of open-label SC abatacept therapy and a 30 day follow-up phone call upon completion of the study. 86 patients will be randomized from approximately 35 centers in the US, Canada and Europe, with the goal of analyzing 74 participants. Our study will test whether abatacept is statistically superior to placebo in reducing the mRSS at month 12 and explore the ability of abatacept to prevent or reverse progression in patients with early disease duration and lower mRSS scores, and reverse established disease in patients with longer disease duration and higher MRSS scores.

The schema below describes the main elements of the study design:

Study design



Escape Therapy

Starting at Month 6, patients with worsening of skin disease (defined as > 5 units worsening of mRSS) have the opportunity to add escape therapy to their randomized study medication (weekly abatacept or placebo SC). In addition, worsening of ILD as defined by absolute decline in FVC% predicted by $\geq 10\%$ or absolute decline in DLCO% predicted by ≥ 15 (confirmed by repeat pulmonary function testing within 1 month) have the opportunity to add escape therapy. Other indications include: active inflammatory polyarthritis or inflammatory myositis. The decision to initiate escape therapy is based on investigator discretion in eligible participants. This may include methotrexate, mycophenolate mofetil, cyclophosphamide, hydroxychloroquine, azathioprine or intravenous immunoglobulin (IVIG). This may not include other biologic therapies.

Should a subject worsen at 3 months, the PI may decide that escape therapy should be initiated immediately. If this occurs, the subject must be withdrawn from study medication. If the subject agrees

to continue study follow up (through month 12), participating in visits and procedures, and complying with blood/tissue collection, the subject may participate in the open label phase.

4.2 Study Population

Before any study procedures are performed, participants will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if participants consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

For entry into the study, the following criteria **MUST** be met:

4.2.1 Inclusion Criteria

1. Signed Written Informed Consent
2. Diagnosis of SSc, as defined using the 2013 American College of Rheumatology/ European Union League Against Rheumatism classification of SSc
3. dcSSc as defined by LeRoy and Medsger
4. Disease duration of ≤ 36 months (defined as time from the first non-Raynaud phenomenon manifestation)

For disease duration of ≤ 18 months

- ≥ 10 and ≤ 35 mRSS units at the screening visit

For disease duration of >18 -36 months

- ≥ 15 and ≤ 45 mRSS units at the screening visit **and** one of the following:
 1. Increase ≥ 3 in mRSS units compared with the last visit within previous 1–6 months
 2. Involvement of one new body area with ≥ 2 mRSS units compared with the last visit within the previous 1–6 months
 3. Involvement of two new body areas with ≥ 1 mRSS units compared with the last visit within the previous 1–6 months
 4. Presence of 1 or more Tendon Friction Rub
5. Age ≥ 18 years at the screening visit
 6. If female of childbearing potential (see 4.2.3), the patient must have a negative pregnancy test at screening and baseline visits

7. Oral corticosteroids (≤ 10 mg/day of prednisone or equivalent) and NSAIDs are permitted if the patient is on a stable dose regimen for ≥ 2 weeks prior to and including the baseline visit
8. ACE inhibitors, calcium-channel blockers, proton-pump inhibitors, and/or oral vasodilators are permitted if the patient is on a stable dose for ≥ 2 weeks prior to and including the baseline visit

For entry into the study, the NONE of the following criteria can be met:

4.2.2 Exclusion Criteria

1. Rheumatic disease other than dcSSc; it is acceptable to include patients with fibromyalgia and scleroderma-associated myopathy
2. Limited cutaneous SSc or sine scleroderma at the screening visit
3. Major surgery (including joint surgery) within 8 weeks prior to screening visit
4. Any infected ulcer prior to randomization
5. Treatment with any investigational agent within ≤ 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of the baseline visit
6. Severe (MRSS 3+) skin on the inner aspects of thighs, upper arms, and abdomen
7. Previous treatment with cell-depleting therapies, including investigational agents, including but not limited to, CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19, and ABA
8. Anti-CD20, and cyclophosphamide within 12 months prior to baseline visit
9. Use of Intravenous Immunoglobulin (IVIG) within 12 weeks prior to baseline visit
10. Previous treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation
11. Immunization with a live/attenuated vaccine within ≤ 4 weeks prior to the baseline visit
12. Treatment with methotrexate, hydroxychloroquine, cyclosporine A, azathioprine, mycophenolate mofetil rapamycin, colchicine, D-penicillamine, within ≤ 4 weeks prior to the baseline visit
13. Treatment with etanercept within ≤ 2 weeks, infliximab, certolizumab, golimumab, ABA or adalimumab within ≤ 8 weeks, anakinra within ≤ 1 week prior to the baseline visit
14. Pulmonary disease with FVC $\leq 50\%$ of predicted, or DLCO (uncorrected for hemoglobin) $\leq 40\%$ of predicted at the screening visit
15. Pulmonary arterial hypertension (PAH) as determined by right heart catheterization or on PAH approved medications for PAH. It is acceptable to use PDE-5 inhibitors for Raynaud's and digital ulcers.

16. Subjects at risk for tuberculosis (TB). Specifically excluded from this study will be participants with a history of active TB within the last 3 years, even if it was treated; a history of active TB greater than 3 years ago, unless there is documentation that the prior anti-TB treatment was appropriate in duration and type; current clinical, radiographic, or laboratory evidence of active TB; and latent TB that was not successfully treated (≥ 4 weeks).
17. Positive for hepatitis B surface antigen prior to the baseline visit
18. Positive for hepatitis C antibody, if the presence of hepatitis C virus was also shown with polymerase chain reaction or recombinant immunoblot assay prior to baseline visit
19. Any of the following prior to the baseline visit:
 - Hemoglobin < 8.5 g/dL;
 - WBC $< 3,000/\text{mm}^3$ ($< 3 \times 10^9/\text{L}$);
 - platelets $< 100,000/\text{mm}^3$ ($< 3 \times 10^9/\text{L}$);
 - serum creatinine $> 2 \times \text{ULN}$; or
 - serum ALT or AST $> 2 \times \text{ULN}$
20. Any other laboratory test results that, in the opinion of the investigator, might place a participant at unacceptable risk for participation in the study.
21. The following medical history and concurrent diseases:
 - Subjects who are impaired, incapacitated, or incapable of completing study-related assessments.
 - Subjects with active vasculitis of a major organ system.
 - Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic, or cerebral disease, whether or not related to SSc and which, in the opinion of the investigator, might place a participant at unacceptable risk for participation in the study.
 - Subjects with a history of cancer in the last 5 years, other than non-melanoma skin cell cancers cured by local resection or carcinoma in situ. Existing non-melanoma skin cell cancers should be removed, the lesion site healed, and residual cancer ruled out before administration of the study drug.
 - Subjects who currently abuse drugs or alcohol.

- Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infections at the time of potential enrollment, including participants with evidence of human immunodeficiency virus (HIV) detected during screening.
- Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months prior to screening.
- Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (e.g., chronic pyelonephritis, osteomyelitis, or bronchiectasis).

22. Patients with a history of anaphylaxis to abatacept

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and to ensure that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

4.2.3 Reproductive Status

Definition of Women of Child-Bearing Potential (WOCBP). WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not post-menopausal. WOCBP therefore includes women using the following methods to prevent pregnancy: Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides); women who are practicing abstinence; and women who have a partner who is sterile (e.g., due to vasectomy).

The following women are defined as post-menopausal:

- Women who have had amenorrhea for ≥ 12 consecutive months (without another cause)
- Women who have irregular menstrual periods and a documented serum FSH level > 35 mIU/mL as part of her medical history.
- Women who are taking hormone replacement therapy (HRT).

WOCBP must be using an acceptable method of contraception to avoid pregnancy throughout the study and for 14 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized.

Acceptable methods of contraception are listed below.

- Hormonal methods: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)

- Barrier and mechanical methods: intrauterine device (IUD); intrauterine hormone-releasing system (IUS), male or female condom with or without spermicide; cap, diaphragm or sponge with spermicide
- Bilateral tubal occlusion
- Vasectomised partner (provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success of the vasectomy)
- True abstinence (where abstinence is a lifestyle choice made by the subject and not only for the duration of the trial)

Periodic abstinence (for example, calendar, ovulation, symptom-thermal and post ovulation methods), abstinence for the duration of the trial and the withdrawal method are not considered acceptable forms of contraception.

WOCBP must have a negative serum or urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of HCG) within 0 to 48 hours before the first dose of study drug.

Women must not be breast-feeding.

4.2.4 Discontinuation of Subjects from Treatment

Subjects **MUST** discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (participant's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Pregnancy
 - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Anaphylaxis or serious allergic reaction

All participants who discontinue should comply with returning to the clinic for an Early Termination visit 30 days post last dose of study drug as outlined in Section 6. For subjects whom cannot comply with returning to the clinic, then a follow up phone call should occur 30 days post last dose. The only exception to this requirement is when a participant withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a participant withdraws before completing the study, the reason for withdrawal must be documented appropriately.

5 TREATMENTS

5.1 Study Treatment

Definition of Investigational Product: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In this protocol, the investigational product is abatacept.

Definition of Non-Investigational Product: Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care. In this protocol, the non-investigational products are medications used for the management of their comorbidities.

5.1.1 Identification

Table 4.1-1: Product Description:

Product Description and Dosage Form	Route of Administration	Potency	Appearance	Storage Conditions (per label)
Abatacept Injection	Subcutaneous	125mg/syringe (125mg/mL)	Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated, 2-8 deg C (36 – 46 Deg F); protect from light; protect from freezing)
Placebo for Abatacept Injection	Subcutaneous	125mg/syringe (125mg/mL)	Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on	Store refrigerated, 2-8 deg C (36 – 46 Deg F); protect from light; protect from freezing)

Table 4.1-1: Product Description:

			visual inspection	
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5.1.2 Handling and Dispensing

- The investigational product should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study participants and only from official study sites by authorized personnel, as dictated by local regulations.
- The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity), as described below:
- Abatacept SC formulations (prefilled syringes) and corresponding placebo should be stored under refrigeration (approximately 2 to 8°C) and protected from long-term (more than 24 hours) exposure to light. Do not freeze.
- Abatacept injection, 125 mg/syringe (125 mg/mL) and placebo for SC administration are ready to use solutions provided in pre-filled siliconized syringes with a 29 gauge needle.
- Care should be taken when handling the injectable drug products that are used in this protocol. Proper aseptic techniques must be used when preparing and administering sterile parenteral products such as abatacept. Parenteral drug products should be inspected visually for particulate matter prior to administration. Refer to the Package Insert for additional information regarding handling, preparation, and storage of abatacept.
- If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact the DCC immediately.

5.2 Drug Ordering and Accountability

5.2.1 Initial Orders

After site activation occurs, the initial drug supply will be sent to the site.

5.2.2 Re-Supply

Subsequent drug supply will be shipped to the site based on site activity.

5.3 Method of Assigning Subjects to Treatment

Patients will be randomized after all screening assessments have been completed and the investigator has verified that eligibility criteria have been met. At the time of randomization, patients will be assigned a unique randomization number; no participant may begin treatment prior to randomization. Eligible participants will be randomized to abatacept or placebo in a 1:1 manner, stratified by dcScc disease duration (≤ 18 months vs >18 to ≤ 36 months). The DCC will

prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the coordinators to enter participant information (e.g., participant ID, stratification factor(s)) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the site pharmacists.

5.4 Selection and Timing of Dose for Each Subject

The recommended dosage is 125 mg/mL single-dose prefilled glass syringe for subcutaneous injection. The injection can be given in front of the thighs, abdomen (except for the 2 inch area around the navel), or the outer area of the upper arms. Arms should be performed by caregiver for risk of injection the deltoid muscle. The medication will be given on weekly basis for a period of 12 months.

For a SAE, the dose may be interrupted until the SAE is resolved. The decision to restart the investigational drug after an SAE will be local investigator responsibility. For other AEs, the investigator will decide on the appropriate action.

5.5 Blinding/Unblinding

- This is a double-blind study. The study staff (except for select staff at the Data Coordinating Center) and the patient are blinded to the treatment assignment.
- Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in a participant, **in which knowledge of the investigational product is critical to the participant's management**, the blind for that participant may be broken.
- Before breaking the blind of an individual participant's treatment, the investigator should have determined that the information is necessary, i.e., that it will alter the participant's immediate management. A discussion with the protocol chairs is encouraged prior to proceeding with unblinding. The investigator holds sole responsibility for the decision to unblind in case of emergency. In many cases, particularly when the emergency is not investigational product-related, the problem may be properly managed by assuming that the participant is receiving active product without the need for unblinding.

5.6 Concomitant Treatments

Patients are allowed to take their medications for underlying comorbidities. Though patients must have a stable dose of prednisone or equivalent (≤ 10 mg/day) and non-steroidal anti-inflammatory agents to enter the study the dosage may change after the baseline visit as the local investigator determines. Prohibited and/or Restricted Treatments

Concurrent administration of a TNF antagonist with abatacept has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone. Concurrent therapy with abatacept and TNF antagonists is not recommended.

The use of live vaccination during the trial and for three months after the last dosage administration is not permitted.

5.6.1 Other Restrictions and Precautions

Serious infections, including sepsis and pneumonia, have been reported in patients receiving abatacept. Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease could further predispose them to infection. Physicians should exercise caution when considering the use of abatacept in patients with a history of recurrent infections, underlying conditions which may predispose them to infections, or chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment with abatacept should be monitored closely. Administration of abatacept should be discontinued if a patient develops a serious infection. For additional information, see Warnings and Precautions section 5.1 of the package insert (Appendix I).

From Abatacept Package Insert (section 5.1):

Concomitant Use with TNF Antagonists

In controlled clinical trials in patients with adult RA, patients receiving concomitant ORENCIA and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively) [see Adverse Reactions (6.1) from package insert]. These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonist; therefore, concurrent therapy with ORENCIA and a TNF antagonist is not recommended. While transitioning from TNF antagonist therapy to ORENCIA therapy, patients should be monitored for signs of infection.

5.7 Treatment Compliance

Patients will be asked to maintain diaries to record medication taken at home. These diaries will be reviewed by the coordinators at each visit to assess compliance.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Study Outcome Assessments

Study-related procedures and outcome measures that will be performed as part of this protocol are listed below. Specific times at which each test will be performed are summarized in the time and events table (section 6.2).

- **Complete medical history.** Medical history will be performed as per standard medical care.

- **Physical examination.** A standard complete physical examination will be performed, with the addition of the assessment of modified Rodnan Skin Score, 28-tender joint count, 28-swollen joint count, tendon friction rubs, joint contractures, digital ulcers and skin examination for cancer. (See section 6.4).
- **Vital signs.** Vital signs will include: pulse, blood pressure, respiratory rate, temperature (C °), height (cm), and weight (kg).
- **Pulmonary function tests (PFTs)**
 1. Spirometry: Carried out by either certified pulmonary function technologists (National Board of Respiratory Care) or experienced staff that meets American Thoracic Society (ATS) recommendations⁶¹⁻⁶⁴. All spirometry equipment and procedures will conform to the most recently published standards of the ATS/ERS Task Force. Forced expiratory maneuvers will be performed at least in triplicate with the minimal requirement that three maneuvers are “acceptable” and that two of these maneuvers meet end-of-test and repeatability criteria for FVC and FEV1.
 2. Single-breath diffusing capacity for carbon monoxide (DLCO): performed in accordance with recently published ATS/ERS guidelines using equipment and testing techniques that meet ATS/ERS requirements⁶¹. At least 2 acceptable tests that meet repeatability criteria will be performed and the mean DLCO value (uncorrected for hemoglobin) from acceptable measurements will be reported.
- **Scleroderma Autoantibodies:** The antibody detection experiments will be performed in the divisional laboratories of the University of Texas Health Science Center at Houston, which is also the lead site for the NIH funded Scleroderma Family Registry and DNA Repository using plasma. Anti-nuclear antibodies and anti-centromere antibodies will be detected by indirect immunofluorescence using HEp-2 cell substrates (Antibodies Inc., Davis, CA, USA). Anti-topoisomerase I, anti-Ro, anti-La, and anti-ribonucleoprotein antibody testing will be performed by passive immunodiffusion against calf thymus extract (Inova Diagnostics, San Diego, CA). Anti-RNA polymerase III antibodies will be determined by enzyme-linked immunosorbent assay (MBL, Nagoya, Japan). Furthermore, less common SSc-related antibodies, anti-fibrillarin, Th/To, PM/Scl-75, and PM/Scl-100 antibodies will be detected by a line immunoassay (LIA: EUROLINE, Euroimmun, Lubeck, Germany).
- **Skin Biopsy:** We will perform two 3-mm skin biopsies at baseline, 3, and 6 months. The skin biopsies are required for participation. They will be shipped to Boston University, where one of the biopsies from each visit will be shipped in batches to Dartmouth University.

- **Blood samples:** 50 ml of blood will be obtained from all study participants at baseline, 1, 3 and 6 months, and shipped from participating centers to the University of Michigan by an overnight express shipping service in insulated shipping containers.

6.2 Schedule of Evaluations

Study Period	Screening	Double-Blind Treatment						Open-Label Treatment			End of Study ^l (Phone call)
		Baseline	Month 1	Month 3	Month 6	Month 9	Month 12 ^j	Month 14	Month 16	Month 18	
Study Week	≤ -4	0	4	12	24	36	48	56	64	72	76
Study Day	-28 to -1	0	28	84	168	252	336	392	448	504	534
Window (in days)		0	(±10)	(±10)	(±10)	(±10)	(±10)	(±10)	(±10)	(±10)	(±10)
Informed Consent	X										
Eligibility (Inclusion/Exclusion) Assessment	X										
Demographics	X										
Medical History	X										
SAFETY ASSESSMENTS											
Physical Exam	X		X	X	X	X	X	X	X	X	
Skin examination for cancer ^k	X		X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	
Laboratory Tests ^a											
CBC, Differential, Comp Panel	X			X	X	X	X	X	X	X	
ESR	X			X			X			X	
PPD/QuantiFERON/TSpot	X										
Pregnancy Test ^b	X	X	X	X	X	X	X	X	X	X	
Hepatitis B and C	X										
Blood Collection for biomarkers (50 mL) ^c		X	X	X	X						
Skin Biopsy ^d		X		X	X						
Echocardiogram and Chest HRCT ^e	X *if available						X *if available				
Pulmonary Function Tests ^f	X				X		X			X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X

Study Period	Screening	Double-Blind Treatment						Open-Label Treatment			End of Study ^l (Phone call)
		Baseline	Month 1	Month 3	Month 6	Month 9	Month 12 ^j	Month 14	Month 16	Month 18	
Study Week	≤ -4	0	4	12	24	36	48	56	64	72	76
Study Day	-28 to -1	0	28	84	168	252	336	392	448	504	534
Window (in days)		0	(±10)	(±10)	(±10)	(±10)	(±10)	(±10)	(±10)	(±10)	(±10)
EFFICACY ASSESSMENTS											
mRSS	X ^h	X	X	X	X	X	X	X	X	X	
Joint Count, digital ulcer assessment, joint contractures, tendon friction rubs	X	X	X	X	X	X	X	X	X	X	
Patient Reported Outcomes ^g		X		X	X		X			X	
Exploratory outcomes ⁱ		X		X	X		X			X	
CLINICAL DRUG SUPPLIES											
Randomization		X									
Study Drug Supplied		X	X	X	X	X	X	X			
Study Drug Adherence			X	X	X	X	X	X	X	X	

^a All laboratory samples will be analyzed at local lab

^b For women of child-bearing potential

^c Out of the 45 mL, 10 mL will be used for proteomics analysis, 5 mL will be collected in PAXgene tubes for RNA analysis, 29.5 mL will be used for flow cytometry, and 0.5 mL for autoantibody measurement

^d Two 3-mm skin biopsies will be collected.

^e Echocardiogram HRCT of Chest is part of standard of care assessments to be performed at the discretion of the PI. The data should be abstracted from the patient records at Screening and month 12. Test results from 6 months prior are acceptable.

^f Spirometry with DLCO

^g All Patient-reported outcomes include patient's and physician's global assessment, PROMIS-29 2.0, SHAQ-DI, PROMIS fatigue scale, PROMIS sleep disturbance and impairment scales, UCLA GIT 2.0 and the PRO-SRSS

^h mRSS will be assessed as one of the inclusion criteria

ⁱ Patient interference with the skin involvement and pain intensity

^j Should a subject terminate early the subject will be brought in to complete all assessments included at the Month 12 visit. Study drug however would not be provided but

returned at that time.

^k This skin evaluation will be an assessment of a need for referral to dermatology for formal cancer evaluation and will be assessed alongside every physical exam.

^j **End of Study:** A Follow up Phone Call should occur 30 days post completion of OLE (18 month visit) or 30 days post End of double blind (12 month study) should participant decides not to enter OLE. Additionally, when a participant discontinues drug, a 30-day post last dose Early Term visit is scheduled; if the participant is unable or unwilling to return, a 30 day follow up phone call will suffice.

6.3 Safety Assessments

All participants who receive a dose of abatacept will be evaluated for safety. Safety outcomes include adverse events, clinically significant changes in vital signs, laboratory test abnormalities, and clinical tolerability of the drug. The investigator will determine the severity of each adverse event as mild, moderate, severe, or very severe. Laboratory findings that the investigator feels are clinically relevant should be recorded as adverse events. In addition, the investigator will determine the relationship of the adverse event to the administration of the study drug. Any occurrence of an AE/SAE from time of consent forward, up to and including follow-up visits will be reported. See Section 7 for the SAE Efficacy Assessments

6.4 Efficacy Assessments

6.4.1 Primary Efficacy Assessments

The **Modified Rodnan skin score** is a validated physical examination method for estimating skin induration. It is correlated with biopsy measures of skin thickness and reflects prognosis and visceral involvement, especially in early disease^{2, 4}. It is scored on a 0 (normal) to 3+ (severe induration) ordinal scales over 17 body areas, with a maximum score of 51 and is used to categorize severity of SSc. It has been extensively used as primary/ secondary outcome in RCTs⁶⁵⁻⁶⁷. This will be collected at every study visit.

6.4.2 Secondary Efficacy Assessments

- **28-Tender joint count:** Investigator will assess tenderness of the joints and score them as positive or negative. The joints include: proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, shoulders, and knees. Performed at every visit.
 - **28-Swollen joint count:** Investigator will assess swelling of the joints and score them as positive or negative. The joints include: proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, shoulders, and knees. Performed at every visit.
 - **Patient global assessment for overall disease:** This assessment represents the patient's assessment of the patient's global scleroderma on a 0-10 Likert scale. "On a scale of 0-10, how was your overall health in the last week? 0=Excellent; 10=Extremely Poor. Assessed at baseline and months 3, 6, 12 and 18.
 - **Physician global assessment for overall disease:** This assessment represents the physician's assessment of the patient's current disease activity on a 0-10 Likert scale. "On a scale of 0-10, how was your patient's overall health in the last week? 0=Excellent; 10=Extremely Poor" . Assessed at baseline and months 3, 6, 12 and 18.
- PROMIS-29 Profile v2.0 measure:** The National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS®) Roadmap initiative (www.nihpromise.org) is a cooperative research

program designed to develop, evaluate, and standardize item banks to measure patient-reported outcomes (PROs) across different medical conditions as well as the US population. PROMIS-29 Profile v2.0 measure contains 29 items, which includes four items each from physical function, anxiety, depression, fatigue, sleep disturbance, pain interference, and satisfaction with social roles domains, and a single item on pain intensity. With the exception of physical function which does not include a time frame, all item banks reference the past 7 days. It is part of the NHLBI-funded RCT of cyclophosphamide vs. mycophenolate mofetil in SSc-associated interstitial lung disease (SSc-ILD). Assessed at baseline and months 3, 6, 12 and 18.

- **SHAQ-DI:** The SHAQ-DI is a disease-targeted, musculoskeletal-targeted measure intended for assessing functional ability in arthritis. It is a self-administered 20-question instrument that assesses a patient's level of functional ability and includes questions that involve both upper and lower extremities. The SHAQ-DI score ranges from 0 (no disability) to 3 (severe disability). It has a 7 day recall period and has been extensively used in SSc^{65, 67}. 5 visual analog scales are included in the scleroderma-HAQ assessing burden of digital ulcers, Raynaud's, gastrointestinal involvement, breathing, and overall disease⁶⁸. Assessed at baseline and months 3, 6, 12 and 18.
- **PROMIS Fatigue measure:** Apart from assessing the PROMIS-29 measure that assesses overall HRQOL, we will assess fatigue as it is one of the common symptoms of patients with SSc. We will administer 8-item short form with 1-week recall (available at www.nihpromis.org). Assessed at baseline and months 3, 6, 12 and 18.
- **PROMIS sleep disturbance and sleep impairment measures:** Sleep disturbances are rated as the one of the top complaints from the patients with SSc and will be assessed using 8-items each with 1 week recall. (available at www.nihpromis.org). Assessed at baseline and months 3, 6, 12 and 18.
- **UCLA SCTC GIT 2.0:** This validated instrument assesses scleroderma-related gastrointestinal symptoms. It has 7 scales and a final composite score <http://uclascleroderma.researchcore.org>. Assessed at baseline and months 3, 6, 12 and 18.
- **Combined Response Index in Systemic Sclerosis (CRISS):** CRISS is a composite measure for early dcSSc. It is determined in a 2-step process that assesses the probability of deterioration (step 1) and of improvement (step 2), where each probability ranges from 0.0 to 1.0. The first step assesses whether the patient has had a significant decline in renal or cardiopulmonary involvement. The second step assesses the probability of improvement by incorporating changes in the modified Rodnan skin score, percent predicted forced vital capacity (FVC), patient and physician global assessments, and SHAQ-DI over 1 year. Assessed at 6 and 12 months.
- **Percent predicted FVC:** Assessed at Screening and months 6, 12 and 18.

6.4.3 Exploratory Efficacy Assessments

- Patient interference with the skin involvement in the past month on a 0-10 Likert scale. On a scale of 0-10, in the last month how much has your skin involvement interfered with your daily activities? 0=Does not limit activity; 10= Very severe limitation. This will be assessed at baseline and month 3, 6, 12 and 18.
- **Cardiac involvement at 12 months:** New/worsened clinically significant heart disease considered secondary SSc, including any of the following: heart failure requiring hospitalization, new onset pulmonary hypertension requiring specific treatment, pericardial disease requiring intervention or clinical decompensation, and arrhythmias and/or conduction defects requiring treatment).
- New renal crisis at 12 months.
- **Percent predicted DLCO**, corrected for hemoglobin. Assessed at months 6, 12, and 18. The equation used for adjusting predicted DLCO from hemoglobin is as follows:

For adult males, the equation (expressing Hb in gm•dL⁻¹) is:

$$D_{L,CO,predicted} \times (1.7Hb / (10.22+Hb))$$

In adult women, the equation is:

$$D_{L,CO,predicted} \times (1.7Hb / (9.38+Hb))$$

- Change from baseline in body mass index at 12 months.
- **Digital ulcer net burden as assessed by the investigator during the trial (after randomization to 12 months):** Digital ulcer net burden is defined as the number of overall digital ulcers as assessed by the investigator. A digital ulcer is defined as an ulcer at or distal to the metacarpophalangeal joint with loss of surface epithelialization. This does not include fissures, cracks or calcium extrusion from calcinosis cutis.
- Pain intensity due to SSc over the past week on a 0-150 mm VAS assessed at baseline, and 3, 6, 12 and 18 months.

6.4.4 Validation of new PRO for Scleroderma-related Skin Symptoms (PRO-SRSS)

Based on findings from a literature review, qualitative focus groups, and consultation with clinical experts, the PRO for Scleroderma-related Skin Symptoms instrument was developed to assess scleroderma-related skin thickening among patients with scleroderma. The instrument focuses on seven skin symptoms: skin tightness, skin thickening, skin sensitivity, skin color, itchiness, pain from skin tightness, and skin puffiness; the baseline version has an additional symptom, skin ulcers. The instrument also assesses limitation to motion of various body parts and has several global items. In the initial assessment, there is a total of 22 items (8 symptom items; 13 limitation in motion items; 1 global severity item), and follow-up version includes 22 items (7 symptom items; 13 limitation in motion items; 1 global severity; and 1 global rating of change in skin symptoms). The PRO-SRSS has a 7-day recall. The PRO-SRSS will be administered at baseline and at the 3, 6, 9 and 12 month visits.

7 ADVERSE EVENT REPORTING

7.1 Adverse Events

An *Adverse Event (AE)* is defined as

- Any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation participant administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.
- Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

7.1.1 Serious Adverse Events

A *Serious Adverse Event (SAE)* is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the participant or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. Potential drug induced liver injury (DILI) is also considered an important medical event (see Section 7.6 for the definition of potential DILI).

- Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

If any SAE occurs the investigator will report it to the Sponsor (via DCC) within 24 hours of their being made aware of the SAE. Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs (See Section 7.5 for reporting pregnancies).

NOTE: The following hospitalizations are not considered SAEs in this study:

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

7.1.2 Non-serious Adverse Events

Non-serious adverse events are all adverse events that are not classified as SAEs.

7.1.3 Assignment of Adverse Event Intensity and Relationship to Abatacept

All adverse events, including those that are serious, will be graded by the investigator as follows:

- Mild (Grade 1): awareness of event but easily tolerated
- Moderate (Grade 2): discomfort enough to cause some interference with usual activity
- Severe (Grade 3): inability to carry out usual activity
- Very Severe (Grade 4): debilitating; significantly incapacitates participant despite symptomatic therapy.
- Death (Grade 5): Death related to AE

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship between the investigational product administration and the adverse event.

The expression “reasonable causal relationship” is meant to convey in general that there are facts (e.g., evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

7.2 Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. To prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more adverse events.

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the event was administered, it should be recorded in the medical record.

7.2.1 Serious Adverse Event Collecting and Reporting

Following the participant’s written consent to participate in the study, all AE/SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

7.2.2 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. NSAE information should also be collected from the start of a placebo lead-in period or other

observational period intended to establish a baseline status for the participants. NSAEs should be followed to resolution or stabilization, or reported as SAEs if they become serious.

Follow-up is also required for NSAEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

All identified NSAEs must be documented appropriately.

7.3 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the participant to receive specific corrective therapy.

Because some drugs have the potential for drug-related laboratory abnormalities, consider adding language specifying which laboratory parameters require follow up and for how long (eg, until stabilization or resolution).

It is expected that whenever possible, the clinical, rather than the laboratory, term would be used by the reporting investigator (eg, anemia vs low hemoglobin value).

7.4 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

7.5 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the participant unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

7.6 Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 7.2.1 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN), and
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), and
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Considerations:

Previous randomized controlled studies in early dcSSc provide the basis for us to characterize the magnitude of treatment differences we could detect with sample sizes of 74-86 participants with a two-sided Type I error of 5%, 80% power, and a drop-out rate of 15%. The phase 2 randomized controlled trial of recombinant human relaxin vs. placebo in participants studied moderate-to-severe dcSSc patients who are similar to those considered for this study. Khanna et al.⁶⁵ found no statistically significant differences in the change from baseline to week 24 in mRSS between relaxin and placebo. The pooled standard deviation (SD) of the change in mRSS is approximately 7 points. We conservatively selected a larger estimate of the SD for our sample size calculations.

This phase 2 study is primarily sized based on practical considerations, rather than a desired power for a pre-specified difference. We plan to screen approximately 121 participants in order to randomize 86 participants to achieve 74 analyzable participants (assuming a 15% attrition rate). With the proposed sample of 74 participants in the study (37 per treatment group), there is at least 80% power to detect a 24% treatment difference in proportions of participants with adverse events with a two-sided Type I error of 5% and a placebo rate of 70% (two-sample test of binomial proportions, East 5.4). For continuous outcomes, there is at least 80% power to detect an effect size of at least 0.66 with a two-

sided Type I error of 5% with this sample size (two-sample t test, East 5.4). This effect size (treatment difference / pooled SD) translates into a treatment difference in change from baseline to month 12 in mRSS of 5.3 with a SD of 8 points. If the pooled SD or drop-out rate is smaller, then the given sample size would allow for smaller treatment differences to be detected with the same power.

8.2 Analyses

A statistical analysis plan (SAP) will be written for the study, and finalized prior to unblinding of the data, that contains more detailed and complete descriptions of the analyses to be performed.

8.2.1 Analysis Populations

Several analysis sets will be used in the analyses of the data:

- **Safety Population.** The Safety Population is defined as all participants who are randomized and receive at least one dose of study drug. The Safety Population will be used for all safety analyses. Subjects will be analyzed by the treatment received.
- **Efficacy Populations.** The main analysis set for efficacy will be the mITT population, defined as all participants randomized, receiving at least one dose of study medication, and having at least one post-baseline efficacy assessment. Subjects will be analyzed by assigned treatment. Membership in the analysis populations will be determined before study unblinding.

8.2.2 General Approach

Descriptive summary statistics will be derived for all data at baseline, overall and by treatment group. For continuous variables, mean, standard deviation, median, interquartile range, minimum and maximum will be reported. For categorical variables, number and percentages will be reported. Graphical methods will be heavily used in this pilot study to assess the pattern of response over time for key variables and to assess the relationships among variables.

We will summarize the extent of missing data over time for the primary endpoint. We will investigate the missing data mechanism (missing at random, not missing at random), which is important for the validity of our analytic approaches, through exploratory analysis. Exploratory analyses will include plots of the mean profile of mRSS at months 0, 3, 6, 9 and 12 by treatment group for those who have complete data throughout the study and those who don't, as well as plots of the mean change from baseline at months 3, 6, 9, and 12 in mRSS in the two treatments within each group (completers and non-completers). If the plots reveal consistent differences between completers and non-completers within each of the treatment groups, then there is evidence that data are not missing at random.

If data are missing at random, in the secondary analysis for the primary endpoint, we may fit a linear mixed model within a Bayesian framework. In a Bayesian framework, missing data is treated as an additional model parameter to be estimated during model fitting. Missing values are estimated through

an iterative procedure by imputing them multiple times based on the data model established using the most current estimates of the remaining model parameters. If data are not missing at random, the analysis will be expanded to include a model for missing data mechanism using a binary variable indicating whether an observation is missing or not. The complete data model will include the linear mixed model and a logistic regression model linking the probability that an observation is missing to some variables we believe are important in explaining the likelihood of a missing observation (for example, in our case, pain or mRSS at previous time point).

Sensitivity analyses will be carried out to assess the robustness of our conclusions to approaches to deal with missing data.

Two-sided p-values will be reported, and no adjustments for multiplicity will be made. Thus, p-values for secondary and exploratory outcomes will be interpreted with caution.

8.2.3 Safety Analyses

Descriptive summary statistics for adverse and serious adverse events will be reported. Adverse events will be grouped by body system and grade and will be tabulated as numbers and percentages; serious adverse events will be enumerated and described as appropriate. The total number of adverse events of each grade occurring in the two treatment groups by month 12 will be compared using a Fisher's exact test. Poisson regression or comparable non-parametric methods will be used to compare the total number of serious adverse events during the double-blind 12-month period by treatment group. For laboratory and other safety parameters that are continuous, two-sample t-tests or Wilcoxon rank sum tests will be performed to compare the two treatment groups.

8.2.4 Efficacy Analyses

Analysis of the Primary Efficacy Endpoint.

The primary efficacy endpoint is the change from baseline to month 12 in mRSS scores. For the primary analysis, changes in mRSS scores from baseline to month 12 will be compared in the two treatment groups using an ANCOVA model with terms for treatment group, duration of dcSSc disease (stratification factor) and baseline mRSS score. If the assumptions of this parametric model are not met, an alternative non-parametric model will be used. Given that the incorporation of escape therapy after month 3 is an indication of treatment failure, we will use a last-observation-carried-forward approach to reflect the impact of treatment on mRSS at the time just prior to escape therapy. Sensitivity analyses will be used to assess the impact of this approach.

Additional analyses of mRSS will be conducted to understand the time course of study treatment, and escape therapy, on mRSS. We will analyze mRSS data at months 0 (baseline), 3, 6, 9 and 12 using a linear mixed model that includes the fixed effect of time-in-study (expressed as a fraction of a year), the interaction between time-in-study and treatment, duration of dcSSc disease (stratification factor), and

patient specific random effects to account for both heterogeneity among patients and correlation among measurements taken on the same participant. To account for the possibility of escape therapy, we will define an additional variable that indicates whether a patient initiated escape therapy and if so, the time (after month 3) the escape therapy was added to the patient's randomized study medication. The model will account for escape therapy by including, at the time points following the beginning of the patient's escape therapy, an additional interaction term between treatment, escape therapy and time-in-study minus time-since-escape-therapy (both expressed as fraction of a year). To test whether there is a significant difference in the way mRSS changes over time between the two groups, we will simply test whether the interaction term between treatment and time-in-study is significantly different from zero.

If mRSS does not change linearly as a function of time-in-study, we will extend the linear mixed model to include: a polynomial of time-in-study (expressed a fraction of a year) of an appropriate degree, the interaction between treatment and the polynomial of time-in-study, duration of dcSSc disease (stratification factor), patient specific random effects, and for time points following the beginning of the escape therapy, the interaction between treatment, escape therapy and the polynomial of time-in-study minus time-since-escape-therapy (both expressed as fractions of a year). In this case, to test whether there is a significant difference between the two groups in the way mRSS changes over time, we will simply test whether any of the coefficients in the interaction between treatment and the polynomial of time-in-study is significantly different from zero. Given the limited sample size of this phase 2 study, we will carefully assess to the fit of these longitudinal models.

Analyses of Secondary Outcomes.

Analysis for secondary outcome measures will be performed using a similar approach at to that for the primary endpoint. In a first analysis, we will compare the change in each secondary outcome measure from baseline to month 12 between the two treatment groups using an ANCOVA model or its non-parametric counterpart if the model assumptions aren't met. For critical secondary outcomes, a longitudinal model (generalized linear mixed model) comparable to that for the primary endpoint will be fit.

Analyses of Exploratory Outcomes.

Graphical methods will be used to explore the distributions of exploratory outcomes by treatment group, and the inter-relationships among the exploratory outcomes and other efficacy outcomes. Generalized linear models will be fit to more formally assess the impact of treatment on the exploratory outcomes, adjusting for the duration of dcScc (the stratification factor) and other important covariates. Non-parametric methods will be used if distributional assumptions are not met.

Analyses of Ancillary Objective.

Descriptive statistics will be used to summarize the change from baseline in the PRO-SRSS at months 3, 6, 9 and 12. Statistical models will be built to assess the relationship between this new PRO with other clinical and QOL measures in the study to validate its utility in the clinical trials arena.

9 STUDY MANAGEMENT

9.1 Compliance with the Protocol

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.2 Record Retention

9.2.1 Record Retention

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. All original source documents supporting entries in the case report forms must be maintained and be readily available.

The Investigator and the study center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or

designee and/or applicable regulatory authorities. The clinical site's regulatory document binder essential elements should include:

- Subject files containing completed case report forms (eCRFs), informed consents/assents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Package Insert, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee.
- If drug supplies are maintained at the study center, documentation for proof of receipt, study drug accountability records, return of study drug for destruction, final study drug product reconciliation statement, and all drug-related correspondence.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, whichever is longer.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines.

9.2.3 Destruction of Investigational Product

Study drugs are to be destroyed on site upon BMS approval, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

9.3 Study Monitoring

Throughout the course of the study, data will be monitored for accuracy and completeness and study procedures will be monitored for adherence to the protocol and Good Clinical Practices (GCP). In addition to frequent contacts through e-mail and telephone, on-site monitoring visits will be coordinated by the Statistical Analysis of Biomedical and Educational Research (SABER) unit at the University of Michigan. SABER (the Data Coordinating Center for this study) will be responsible for operational aspects and monitoring of the trial, including annual monitoring visits and/or regular remote source data verification. During the on-site visits, the CRFs will be reviewed for completeness and adherence to the protocol, accuracy, consistency of the data, and adherence to local regulations on the conduct of clinical research. The monitor will need access to subject medical records and other study-related records needed to verify the entries on the electronic case report forms. The study monitor will also perform drug accountability checks and review the clinical site's regulatory document binder to assure completeness of documentation in all respects of clinical study conduct.

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the ASSET Steering Committee to monitor participant enrollment, data collection and patient safety, and evaluate the efficacy of this randomized controlled trial of abatacept for the treatment of diffuse cutaneous systemic sclerosis. The Data Safety Monitoring Board will consist of at least 3 members. Members are appointed by the Investigator Sponsor. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the study. The DSMB will meet face to face a minimum of once a year at the call of the Chair. In addition, it likely will meet by conference call at intervals of 6 months following the annual meeting.

A Medical Safety Monitor, a physician with clinical trials experience and expertise in scleroderma who is independent of the conduct of the study, will review all SAEs.

10 NIH DATA SHARING POLICY

The mechanistic study is supported by NIH, NIAID, DAIT. NIH has a data sharing policy and implementation guidance and the study will follow this guidance: http://grants.nih.gov/grants/policy/data_sharing/

The goals of the Immunology database and analysis portal at DAIT, NIAID are to accomplish many of the guidelines outlined in the NIH sharing policy. These include:

- accelerating a more collaborative and coordinated research environment
- creating an integrated database that broadens the usefulness of scientific data and advances hypothesis-driven and generating research
- advancing the pace and quality of scientific discovery while extending the value of scientific data in all areas of immunological research
- promoting rapid availability of important findings, making new discoveries available to the research community for further analysis and interpretation
- providing analysis tools to advance immunological research

11 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

11.1 Use of Stored Samples and Data

Samples and data collected under this protocol may be used to study effect of abatacept on skin and blood gene expression and effect on T-cell biology. No genetic testing will be performed.

11.2 Disposition of Stored Samples and Data

- Access to stored samples will be limited using a locked freezer. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected

computers. Only investigators will have access to the samples and data.

- Samples and data acquired will be kept at University of Michigan. Skin biopsies will be housed at Boston University and Dartmouth University.
- At the completion of the protocol (termination), samples and data will be reserved for future, unspecified research if the subject has consented to analysis of their specimens outside of this protocol. If the subject doesn't consent to long term storage, the samples will be destroyed at the end of the study.
- Additionally, subjects may decide at any point during the study not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol.
- In the future, other investigators (both at UM and outside) may wish to study these samples and/or de-identified data.

12 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor to be related to the investigational product
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the Package Insert), or that could be associated with the study procedures.
SUSAR	Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC).
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved investigational product)

13LIST OF ABBREVIATIONS

AB	Antibody
ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine Transaminase
APC	Antigen-Presenting Cell
ARA	American Rheumatology Association
AST	Aspartate Transaminase
BCG	Bacillus Calmette-Guérin
BMS	Bristol-Myers Squibb
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC-ACID	Centers for Disease Control and Prevention Advisory Committee on Immunization Practices
CFR	Code of Federal Regulations
CI	Confidence Interval
CMV	Cytomegalovirus
CRF	Case Report Forms
CRP	C-Reactive Protein
CTLA	Cytotoxic T-Lymphocyte Associated
CXR	Chest X-Ray
DMARD	Disease-Modifying Antirheumatic Drug
DNA	Deoxyribonucleic Acid
D5W	Dextrose (5%) in Water
EC	European Commission
ESR	Expedited Safety Report
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus

HLA	Histocompatibility Leukocyte Antigen
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
ILD	Interstitial Lung Disease
IND	Investigational New Drug (Application)
IRB	Independent Review Board
IST	Investigator-Sponsored Trial
IU	International Unit
IV	Intravenous
JRA	Juvenile Rheumatoid Arthritis
MHC	Major Histocompatibility Complex
MRI	Magnetic Resonance Imaging
MRSS	Modified Rodnan Skin Score
NPV	Negative Predictive Value
NS	Normal Saline
NSAE	Non-Serious Adverse Event
NSAID	Non-Steroidal Anti-inflammatory Drug
OA	Osteoarthritis
PCR	Polymerase Chain Reaction
PFE	Phosphodiesterase
PPD	Purified Protein Derivative
PPV	Positive Predictive Value
PVC	Polyvinylchloride
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
Se	Sensitivity
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
Sp	Specificity
SUSAR	Suspected Unexpected Serious Adverse Reaction

SWFI	Sterile Water For Injection
TB	Tuberculosis
TNF	Tumor Necrosis Factor
ULN	Upper Level of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

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